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(54) Title: PROCESSES OF PREPARING PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Process of preparing a water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt and water-soluble binder, wherein the process comprises the steps of: (a) admixing ibuprofen and inorganic alkaline salt in particulate form to form a premix; (b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture; and (c) drying the granulated mixture.

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# Processes of Preparing Pharmaceutical Compositions

## Field of the Invention

The present invention relates to processes of preparing a pharmaceutical composition, in particular the present invention relates to processes of preparing a water-soluble pharmaceutical composition comprising ibuprofen.

## Background of the Invention

Ibuprofen (ie. 2-(4-isobutylphenyl) propionic acid) is well known as a therapeutic agent having analgesic, anti-inflammatory and antipyretic activity. It is extensively used as an alternative to aspirin (ie. acetylsalicylic acid) and paracetamol (ie. acetaminophen) in the treatment of pain, such as headache, toothache and especially when associated with inflammation in, for example, rheumatic disease. However, ibuprofen is water-insoluble and often causes gastric irritation when administered in solid or suspended form, especially in the doses required to treat rheumatic disease. Only a few salts of ibuprofen are water-soluble and these include the alkali metal salts and amino acid salts. However, solutions of water-soluble ibuprofen salts have an unpleasant burning taste and, for that reason, their use generally have been avoided. Many attempts have been made to improve the solubility and taste of ibuprofen, especially in its free acid form.

GB-A-2189994 discloses that the low water-solubility of ibuprofen can be overcome by formulation into an effervescent composition consisting of 9 to 17 weight percent ibuprofen; 17 to 33 weight percent arginine or an arginine/lysine mixture containing up to 40 weight percent lysine; 20 to 35 weight percent sodium or potassium bicarbonate; and 25 to 40 weight percent sodium or potassium bitartrate. The presence of arginine is essential and it appears that the ibuprofen must be present as the free acid. In particular, it is stated that arginine and lysine salts of ibuprofen cannot be used because they do not result in the complete dissolution of the ibuprofen.

EP-A-0203768 discloses effervescent compositions of a pre-blended mixture of granulated therapeutic agent and effervescent system component. The

therapeutic agent is required to have a particle size of 100 to 600 micrometres and the effervescent system component is required to have a particle size of 50 to 600 micrometres. Ibuprofen is included amongst numerous specified therapeutic agents and sodium, potassium and ammonium bicarbonate are included amongst the specified effervescent system components.

EP-A-0228164 discloses effervescent ibuprofen-containing compositions which provide an improved suspension of ibuprofen or a salt thereof when added to water. The composition includes a pharmaceutically acceptable surfactant and a pharmaceutically acceptable water-insoluble hydrophilic polymer. Exemplified polymers include starch and derivatives thereof, cellulose and derivatives thereof; cross-linked poly-vinylpyrrolidone and alginic acid. The preferred polymers are microcrystalline cellulose and croscarmellose sodium. Specified base components of the effervescent couple include sodium and potassium bicarbonate. The amounts of the components of the effervescent couple are generally chosen so that the pH of the resultant aqueous suspension is below 7.0, preferably 3.0 to 4.0. Free ibuprofen is preferred but reference is made to the use of the sodium or potassium salt. When the ibuprofen is in the form of such a water-soluble salt, the salt reacts with the acid component of the effervescent couple to cause ibuprofen to precipitate on addition of the composition to water.

GB-A-2193093 discloses water-soluble ibuprofen compositions containing 33-46 weight percent free ibuprofen, 34-51 weight percent L-arginine and 9-29 weight percent sodium bicarbonate. The molar ratio of L-arginine to ibuprofen is required to be in the range 1.1:1 to 1.5:1 and the weight ratio of sodium. GB-A-2193093 refers to the good water-solubility of sodium ibuprofen but teaches against the use of this salt in an oral preparation. In particular, it is stated that:-
"Ibuprofen sodium salts is one of few salts with a good solubility in water, but it is not very suitable for an oral preparation because it gives solutions having a pH which produces gastrointestinal damage."

Example 13 of GM-A-2193093 discloses a comparative granulate containing arginine ibuprofen (37 wt %), sodium bicarbonate (10 wt %) and saccharose (46 wt %). The mole ratio of sodium bicarbonate to arginine ibuprofen is

resulting in a preparation which is stated to be unacceptable both for taste and local tolerability.

JP-A-63198620 discloses non-effervescent ibuprofen compositions containing an antacid and/or mucous membrane covering agent to reduce the risk of digestive disorders. The antacid and/or mucous membrane covering agents specified include sodium bicarbonate but there is no exemplification of compositions including sodium bicarbonate. Further, there is no reference to the use of an ibuprofen salt or to masking the taste of the ibuprofen.

WO 89/03210 discloses that clear, stable and palatable liquid ibuprofen compositions can be obtained by dispersing and suspending, or dissolving, ibuprofen or salts or esters thereof in an aqueous medium containing a methylcelluloses composition. A flavouring agent, especially a sweetening agent, can be present to mask the bitter taste of ibuprofen. Optionally, a bicarbonate, preferably potassium bicarbonate, is present in the aqueous medium to assist dispersion of the ibuprofen. A flavouring agent, preferably sucrose, can be added to mask the taste of the ibuprofen. There is no reference to the use of a bicarbonate with an ibuprofen salt or to non-aqueous preparations containing both ibuprofen and bicarbonate. In the compositions of the Examples, the amount by weight of sucrose is about four times that of potassium bicarbonate except in the composition of Example 6 which contains no bicarbonate. The mole ratios of bicarbonate to ibuprofen are 1.2 (Examples 1,4 & 5) (Example 3) and 19.0 (Example 2).

It would be desirable to further improve the solubility of ibuprofen. It would also be desirable to provide a pharmaceutical composition comprising ibuprofen which is soluble in water to give a clear solution and provides good taste characteristics.

## Summary of the Invention

According to one aspect of the present invention there is provided a process of preparing a water-soluble pharmaceutical composition, the composition

comprising ibuprofen, inorganic alkaline salt and water-soluble binder, wherein the process comprises the steps of:

(a) admixing ibuprofen and inorganic alkaline salt in particulate form to form a premix;
(b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture; and
(c) drying the granulated mixture.

According to the first aspect of the present invention there is further provided a process of preparing an effervescent water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt, water-soluble binder and organic acid, wherein the process comprises the steps of:

(a) admixing ibuprofen and inorganic alkaline salt to form a premix;
(b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture;
(c) drying the granulated mixture; and
(d) admixing the organic acid and the dry granulated mixture.

The process according to the first aspect of the present invention is hereinafter referred to as "wet granulation".

According to a second aspect of the present invention there is provided a process of preparing a water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt and non-aqueous binder, wherein the process comprises the steps of:

(a) admixing ibuprofen and inorganic alkaline salt in particulate form to form a premix; and
(b) granulating the premix together with the non-aqueous binder.

According to the second aspect of the present invention there is further provided a process of preparing an effervescent, water-soluble pharmaceutical composition, the composition comprising ibuprofen,

inorganic alkaline salt, non-aqueous binder and organic acid, wherein the process comprises the steps of:

(a) admixing ibuprofen and inorganic alkaline salt in particulate form to form a premix;
(b) granulating the premix with the non-aqueous binder to form a granulated mixture; and
(c) admixing the organic acid and the granulated mixture.

The process according to the first aspect of the present invention is hereinafter referred to as "dry granulation".

The compositions prepared according to the processes of the present invention exhibit increased solubility in aqueous medium to form clear solutions.

All levels and ratios are by weight of total composition, unless otherwise indicated.

## Detailed Description of the Invention

The process according to the first aspect of the present invention provides a non-effervescent, water-soluble composition comprising ibuprofen, inorganic alkaline salt and water-soluble binder. The process comprises the steps of:

(a) admixing ibuprofen and inorganic alkaline salt to form a premix;
(b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture; and
(c) drying the granulated mixture.

A first essential ingredient of the compositions herein is ibuprofen. The level of ibuprofen is present in the compositions herein at a level of from about 1% to about 20%, preferably from about 1% to about 15%, more preferably from about 1% to about 10% by weight of composition.

A second essential ingredient of the compositions herein is an inorganic alkaline salt. The inorganic alkaline salt is preferably present in the compositions herein at a level of from about 10% to about 90%, more preferably from about 40% to about 80% by weight of composition. Highly preferred compositions herein, however, comprise at least about 50% by weight of inorganic alkaline salt, more especially at least about 60% by weight. Suitable inorganic alkaline salts for use herein include alkali metal carbonates and bicarbonates, and mixtures thereof, for example, sodium carbonate, sodium bicarbonate, sodium sesquicarbonate, potassium carbonate and potasium bicarbonate, preferably a mixture of sodium carbonate and sodium bicarbonate. Alkali metal bicarbonates are also useful herein as taste masking agents.

A third essential ingredient of the compositions prepared according to the process of the first aspect of the invention is a water-soluble binder. The water-soluble binder is preferably present in the compositions herein at a level of from about 0.01% to about 10%, more preferably from about 0.1% to about 5% by weight of composition. The water-soluble binder for use herein is preferably selected from polyvinylpyrollidone, methyl celullose, hydroxypropylmethyl cellulose and hydroxypropylethylcellulose, and mixtures thereof, preferably methyl cellulose and polyvinylpyrollidone.

In the process of the invention the water-soluble binder is present as an aqueous solution. The aqueous solution of the water-soluble binder which is used in the process of the present invention comprises from about 2g to about 10g, preferably from about 3g to about 5g of water-soluble binder per 100ml of water. The water-soluble binder is preferably added to the ibuprofen and inorganic alkaline salt mixture at a level of from about 10% to about 40%, preferably from about 10% to about 30% by weight (levels being by weight of the ibuprofen and inorganic alkaline salt premix).

In order to provide compositions which are effervescent as well as clear on dissolution in water, the compositions further comprise an organic acid.

Hence the first aspect of the present invention further provides a process of preparing an effervescent, water-soluble pharmaceutical composition, the

composition comprising ibuprofen, inorganic alkaline salt, water-soluble binder and organic acid, wherein the process comprises the steps of:

(a) admixing ibuprofen and inorganic alkaline salt to form a premix;
(b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture;
(c) drying the granulated mixture; and
(d) admixing the organic acid and the dry granulated mixture.

Suitable organic acids for use herein include citric acid, tartaric acid, fumaric acid, citric acid, malic acid, maleic acid, gluconic acid, succinic acid, salicylic acid, adipic acid or sulphamic acid, sodium fumarate, sodium and potassium acid phosphates, betaine hydrochloride, and mixtures thereof, preferably citric acid. The organic acid is preferably present in the compositions herein at a level of from about 5% to about 50%, more preferably from about 5% to about 35% by weight of composition. The mixing weight ratio of dry granulated mixture to organic acid is preferably in the range from about 10:1 to about 1:1, more preferably from about 5:1 to about 1:1, especially from about 3:1 to about 1:1.

In the wet granulation process herein the premix of ibuprofen and inorganic alkaline salt preferably comprises from about 1% to about 90%, more preferably from about 1% to about 50%, especially from about 1% to about 20% by weight of ibuprofen and from about 10% to about 99%, more preferably from about 50% to about 99%, especially from about 70 to about 99% by weight of inorganic alkaline salt (levels being by weight of the premix).

It is also possible to prepare water-soluble pharmaceutical compositions under non-aqueous conditions. Hence according to a second aspect of the present invention there is provided a process of preparing a non-effervescent water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt and non-aqueous binder, wherein the process comprises the steps of:

(a) admixing the ibuprofen and inorganic alkaline salt to form a premix; and

(b) granulating the premix together with the non-aqueous binder.

The non-aqueous binder is preferably present in the compositions herein at a level of from about 1% to about 30%, more preferably from about 5% to about 20% by weight of composition. The non-aqueous binder herein is selected from polyethylene glycols of molecular weight of from about 1,000 to about 50,000, polyvinylpyrrolidone, poly(oxyethylene) of molecular weight of from about 20,000 to about 500,000, Carbowax having a molecular weight of from about 4,000 to about 20,000, nonionic surfactants, fatty acids, sodium carboxymethyl cellulose, gelatin, fatty alcohols, phosphates and polyphosphate, clays, aluminosilicates and polymeric polycarboxylates, and mixtures thereof, preferably polyethylene glycols.

According to the second aspect of the present invention there is further provided a process of preparing an effervescent, water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt, non-aqueous binder and organic acid, wherein the process comprises the steps of:

(a) admixing the ibuprofen and inorganic alkaline salt to form a premix;
(b) granulating the premix with the non-aqueous binder to form a granulated mixture; and
(c) admixing the organic acid and the granulated mixture.

In the dry granulation process herein the granulated mixture preferably comprises from about 1% to about 90%, more preferably from about 1% to about 20% by weight of ibuprofen, preferably from about 30% to about 90%, more preferably from about 40% to about 80% by weight of inorganic alkaline salt and preferably from about 1% to about 30%, more preferably from about 5% to about 20% by weight of non-aqueous binder (levels being by weight of granulated mixture).

The dry granulated mixture herein is substantially free of moisture, i.e. it comprises less than about 5%, preferably less than about 1% by weight of the dry granlulated mixture.

The compositions prepared according to the processes of the present invention preferably have an average particle size of from about 50μm to about 700μm, more preferably from about 100μm to about 500μm and especially from about 100μm to about 250μm.

The compositions herein can comprise other optional components such as wetting agents, lubricants such as talc, magnesium stearate, finely divided amorphous pyrogenic silicas, surfactants, chelating agents, enzymes, pigments/dye, colours, flavour oils such as oils of spearmint, peppermint and wintergreen, dyestuffs, sweeteners, foam depressants such as dimethylpolysiloxanes, foam stabilizers such as the fatty acid sugar esters, preservatives, and the like.

The compositions herein can be administered in the form of water-soluble granules, tablets, hot and cold drinks, and the like. The compositions prepared according to the processes of the invention are soluble in water to give a clear solution having a final pH of from about 6 to about 10.

The following Examples illustrate the compositions prepared according to the processes of the present invention.

Examples I - V

A premix of the inorganic alkaline salts and the ibuprofen is prepared as a first step. The following table illustrates the premixes of Examples I-V.

| | I/% | II/% | III/% | IV/% | V/% |
|---|---|---|---|---|---|
| $NaHCO_3$ | 65 | 64.7 | 65 | 70 | 71 |
| $Na_2CO_3$ | 24.5 | 23 | 23 | 25 | 24.6 |
| Ibuprofen | to 100 | to 100 | to 100 | to 100 | to 100 |

The resulting premix is then granulated with 25% by weight of the premix of a 5% w/v methyl cellulose solution. Finally the granulated mixture is dried. To provide effervescent compositions citric acid can be admixed with the dried granulated mixture at a level of 30% by weight of the dried granulated mixture.

The compositions can then be tableted and packaged.

The compositions of Examples I-V exhibit excellent solubility in water to provide clear solutions

Examples VI - X

| | VI/% | VII/% | VIII/% | IX/% | X/% |
|---|---|---|---|---|---|
| $NaHCO_3$ | 77.0 | 58.2 | 16.7 | 44.6 | 44.6 |
| Citric Acid | 0.0 | 0.0 | 28.3 | 16.7 | 33.7 |
| Ibuprofen | 8.0 | 7.0 | 6.7 | 6.7 | 6.6 |
| $Na_2CO_3$ | 0.0 | 19.6 | 33.3 | 28.3 | 0.0 |
| PEG(1) | to 100 | to 100 | to 100 | to 100 | to 100 |

1. Polyethylene glycol of molecular weight 10,000

The above Examples VI - X can be prepared as follows. The ibuprofen is premixed with the inorganic alkaline salts and the resulting premix is granulated with the polyethylene glycol. To provide compositions which are effervescent when mixed with water the organic acid is admixed with the granulated mixture.

The compositions can then be tableted and packaged.

The compositions of Examples VI - X exhibit excellent solubility in water to provide clear solutions.

WHAT IS CLAIMED IS:

1. Process of preparing a water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt and water-soluble binder, wherein the process comprises the steps of:

   (a) admixing ibuprofen and inorganic alkaline salt in particulate form to form a premix;
   (b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture; and
   (c) drying the granulated mixture.

2. Process according to Claim 1 wherein the water-soluble binder is selected from polyvinylpyrollidone, methyl cellulose, hydroxypropylmethyl cellulose and hydroxypropylethylcellulose, and mixtures thereof.

3. Process according to Claim 1 or 2 wherein the ibuprofen is present at a level of from about 1% to about 20%, preferably from about 1% to about 15% by weight of composition.

4. Process according to any of Claims 1 to 3 wherein the inorganic alkaline salt is present at a level of from about 10% to about 90%, preferably from about 40% to about 80% by weight of composition.

5. Process according to any of Claims 1 to 4 wherein the water-soluble binder is present at a level of from about 0.01% to about 10%, preferably from about 0.1% to about 5% by weight of composition.

6. Process of preparing an effervescent, water-soluble pharmaceutical composition, the composition comprising ibuprofen, inorganic alkaline salt, water-soluble binder and organic acid, wherein the process comprises the steps of:

   (a) admixing ibuprofen and inorganic alkaline salt to form a premix;

(b) granulating the premix together with an aqueous solution of the water-soluble binder to form a granulated mixture;
(c) drying the granulated mixture; and
(d) admixing the organic acid and the dry granulated mixture.

7. Process according to Claim 6 wherein the organic acid is present at a level of from about 5% to about 50%, preferably from about 5% to about 35% by weight of composition.

8. Process according to Claim 6 or 7 wherein the mixing weight ratio of dry granulated mixture to organic acid is in the range of from about 10:1 to about 1:1, preferably from about 5:1 to about 1:1.

9. Process according to any of Claims 1 to 8 wherein the pharmaceutical composition has an average particle size of from about 50 μm to about 700 μm, preferably from about 100 μm to about 500 μm, more preferably from about 100 μm to about 250 μm.

10. A pharmaceutical composition comprising a granulated mixture of ibuprofen, inorganic alkaline salt and water-soluble binder wherein the granulated mixture comprises at least about 50% by weight of the inorganic alkaline salt.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/15764

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 9/16, 9/20, 9/46
US CL :424/465, 466, 489

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/465, 466, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,P | US, A, 5,445,827 (FRITSCH ET AL) 29 AUGUST 1995, column 2, line 14 through column 4, line 41. | 1-10 |
| Y | US, A, 4,687,662 (SCHOBEL) 18 AUGUST 1987, column 2, lines 17-27, column 3, line 36, column 4, line 13 through column 6, line 8, column 7, line 1 through column 8, line 29. | 1-10 |

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